REMARKS

In view of the following remarks, the Examiner is respectfully requested to allow Claims 1 to 28, the only claims pending and currently under examination in this application.

The Examiner is thanked for the helpful interview held with the undersigned and Dr. Bradley Galer on October 2, 2007. During the interview, the above amendments were discussed with the Examiner in view of the office action and cited references. The Examiner indicated that the above amendments would appear to overcome the issues raised in the current office action, but that a final determination would require review of the submitted response. It is believed that the above discussion provides an accurate summary of the substance of the interview.

Amendment to the Claims

Claim 1 has been amended clarify the wording of the claim. In addition, Claims 1, 6 and 11 have been amended to reinforce the meaning of topical delivery as being limited to only local delivery of the active agent. Support for this amendment can be found on page 10, line 5, of the specification as originally filed which reads in relevant part: "the subject methods are amenable to self-administration and do not give rise to systemic side effects, since the active agent only acts locally." See also page 7, lines 19-23 of the specification as originally filed. As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, 2nd ¶

Claims 1-28 have been rejected for use of the phrase "at least ameliorating." Upon review of the claims, Claim 1 is the only claim that includes this phrase. With respect to Claim 1, this phrase has been amended and the language further clarified in accordance with the suggestion of the Examiner. Accordingly, this rejection may be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 1-28 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Freidman (U.S. Patent No. 6,139,861) in view of Oda et al. (U.S. Patent No. 5,725,874).

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. *See Pharmastem Therapeutics v. Viacell et al.*, 2007 U.S. App. LEXIS 16245 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (*citing KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007))); *and see Omegaflex, Inc. v. Parker-Hannifin Corp.*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) ("[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (*citing KSR Int'l Co.* at 1741)); *and see Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006) ("[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,'" (*citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004))).

An element of the rejected claims is the step of topically applying an effective amount of a "topical formulation" of an NSAID to: "a keratinized skin surface of the head of said host," (Claim 1); "a keratinized skin surface of at least one of the forehead and temples of said mammal," (Claim 6); and " at least one of the forehead, temples

and/or occipital region of said human," (Claim 11).

All of these specified regions of application would be sites of local topical delivery of an agent only, where no clinically meaningful systemic drug levels are achieved. "**Topical**" drug products are understood to mean by those of skill in the art as non-systemic drug products. As such, topical formulations are known by those of ordinary skill in the art as formulations that produce their clinical effect by interacting with the skin, soft-tissue, and/or nerves directly underlying the keratinized skin where the drug is applied. Topically applied formulations are also known by those of ordinary skill in the art as ones that do not result in any clinically meaningful blood levels, and do not produce any systemic side effects.

Evidence that the phrases "topically applying" and "topical formulation" refer to local delivery and not system delivery mechanisms include the following publications. Galer & Dworkin, A Clinical Guide to Neuropathic Pain (McGraw-Hill, 2000) includes the following definition of topical delivery at page 57:

> A true topical analgesic has the following
> haracteristics:
> - The medication is applied directly to the skin overlying the painful region.
> - The medication penetrates the skin effectively.
> - The site of the mechanism of action is local activity in the peripheral tissues, such as the peripheral nociceptors in the skin.
> - No clinically significant systemic blood levels can be measured.

Similarly, **Galer BS**, Gammaitoni A, Alvaraz, N. Pain. Scientific American Medicine, WebMD. 2001, Chapter 10, Section XIV. provides the following description of topical delivery at page 22:

Topical drugs are applied to the skin at the site that overlies the painful region of the body. The drug penetrates the skin and acts on the peripheral tissues, nerves, and soft tissues directly underlying the skin. The rate of delivery of the active medication can be well controlled through use of the optimal vehicle for topical drug delivery and use of the optimal matrix controls. The ideal topical formulation would achieve local concentration sufficient to produce a local effect without producing clinically relevant systemic blood levels. (A comparison of the properties of topical and transdermal drug delivery systems is presented [*see Table 9*].) Excessive drug absorption may cause local specificity to be lost, allowing a drug to be distributed systemically to undesired sites.

Similarly, the "Topical Drugs for the Treatment of Pain" chapter in the premiere pain textbook *Bonica's Managment of Pain*. (**Galer BS**. Topical Drugs for the Treatment of Pain. In: Loeser, JD: *Bonica's Managment of Pain*. 2000) provides the following description of topical delivery at page 1737:

BASIC INFORMATION

Topical medications (Table 87-1) are applied directly on the painful body area, where they penetrate the skin. A topical medication's site of activity is in the peripheral tissues, including soft tissue and peripheral nerve, directly underlying the site of application. Topical drugs, formulated as a gel, cream, liquid, or patch, should not produce any clinically significant systemic drug concentration.

Yet more evidence that those of skill in the art equate topical delivery with local delivery is found in the attached Radcliffe Letter to the FDA which includes the statement:

> Thus for non-systemic drug products, such as topical and ophthalmic drugs, MMA allows for a determination of bioavailability based solely on the rate and extent to which the active ingredient becomes available at the site of drug action. No demonstration or evaluation of systemic absorption is required.

As such, one of skill in the art reading the present claims of the application would read the above recited locations of topical drug delivery as being locations in which the active agent is only locally delivered to the subject without systemic activity. One of skill in the art would not read these claims and locations as providing systemic delivery of agent.

As will be demonstrated below, the combined teaching of the cited references fails to teach or suggest at least the claim elements of topically applying an effective amount of a topical NSAID formulation to: "a keratinized skin surface of the head of said host," (Claim 1); "a keratinized skin surface of at least one of the forehead and temples of said mammal," (Claim 6); and " at least one of the forehead, temples and/or occipital region of said human," (Claim 11).

One of skill in the art would read Friedman as only teaching intraoral delivery of a formulation. One of skill in the art would so read Friedman because at Col. 3, lines 40 to 52; Friedman states:

> In accordance with the invention, the topical application of a combination of at least one member of anti-inflammatory medication(s) (NSAID and or a glucocorticoid steroid), dissolved, dispersed or distributed in a suitable carrier useful in delivering and enabling adherence of the medication to the mucous membrane of the mouth is formulated. The invention also embodies specific placement of this composition (anti-inflammatory agent and carrier) to the periapical areas of the posterior molar teeth (the area of maxillary alveolar tenderness), in cases of migraine, tension-type headache, post-traumatic headache, facial pain and cervical muscle spasm. The compositions can be applied in

As described by Friedman, his invention only claims that applying an NSAID to the "zone of intraoral inflammation localized in the maxillary third molar apical area...correlating the plexus formed by the posterior superior alveolar branch of

the ipsilateral maxillary nerve" for headache pain "associated with a zone of intraoral inflammation." Friedman also specifically states "The treatment location is also significant" (column 3, line) and "The object of this invention is to reduce or eliminate this intraoral inflammation localized in the maxillary third molar apical area..." (column 3, lines 29-32). Thus, Friedman does not claim nor describe topical application of NSAID on keratinized skin of the head, but rather specifically only claims intraoral medication application affecting the underlying nerve structure in the mouth, jaw, and dentition [see http://www.maxfaxsho.co.uk/index_files/Page4811.htm].

Thus, application of an NSAID as described by the claims of Friedman are anatomically and functionally distinct from that specified in the present claims. Because the exact placement of the formulation is critically important in Friedman for the active medication to produce the desired clinical effect, one of skill in the art would not have supposed or attempted to treat headaches by topical application of keratinized skin of the head, forehead, temple and/or occiput based upon the teachings of Friedman.

Furthermore, it is well known by those experienced in the art of drug delivery that application of a drug to the intraoral mucous membranes likely results in systemic delivery of an active agent. As Friedman himself writes "The rate of absorption through the mucous membrane is rapid." Applying drugs, even in a small surface area, to the oral mucous membranes results in rapid delivery of drug to the systemic circulation due to the highly vascular nature of the intraoral mucosal tissues. As stated in an industry report "...the permeability of mucous membranes provides a convenient route for the **systemic** delivery of new and existing therapeutic drugs. Transmucosal delivery offers the potential for once daily dosing of oral drugs and avoids the effects of first pass metabolism." [www.medicalnewstoday.com/articles/65620.php] A report from the University of Alberta that was published in J Pharm Pharmaceut Sci 1 (1):15-30, 1998 states:

"Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable." Furthermore, this report outlines the cellular structure and characteristics of the oral mucosa, which are dramatically distinct from that of keratinized skin.
[http://www.ualberta.ca/~csps/JPPS1(1)/A.Shojaei/buccalreview.htm]

Thus, Friedman only teaches intraoral transmucosal delivery of drug which will likely result in **systemic** delivery to a subject.

One of skill in the art would read Oda as describing "percutaneously absorbed formulations" for systemic delivery only. Oda's externally applied formulations are aimed to produce clinically meaningful systemic (blood) levels, since the vast majority of the drug classes listed in Oda only have a clinically meaningful effect if they enter the circulation in clinically significant amounts, such as central nervous stimulants, hormones, antihypertensive agents, cardiotonics, antiarrhythmic agents, coronary vasodilators, antineoplastic agents, antiepileptics, anti-parkinson agents, assistant to the prohibition of smoking, and vitamins. These agents are listed at Col. 2, line 52 to Col. 3, line 27. Thus Oda teaches solubilizers that when added to formulations applied to the skin improve and enhance delivery of active medication into systemic circulation.

Because Freidman teaches only intraoral transmucosal delivery of active agent, and Oda's disclosed formulations would be read by those of skill in the art as being disclosed for systemic delivery of active agent, the combined teaching of the references fails to teach or suggest the claim elements of topically applying an effective amount of a **topical** NSAID formulation to: "a keratinized skin surface of the head of said host," (Claim 1); "a keratinized skin surface of at least one of the forehead and temples of said mammal," (Claim 6); and " at least one of the forehead, temples and/or occipital region of said human," (Claim 11). These claim elements are not

taught or suggested because they are known by those of skill in the art as not being methods of systemic delivery of an active agent. Furthermore, these claim elements are not taught or suggested by either Friedman and/or Oda as neither describes or comments on having the sole mode of action of an NSAID localized only in the underlying tissues and nerves beneath the keratinized skin of the head, forehead, temples and/or occipital region where the topical NSAID is applied.

As such, the combined teaching of Freidman in view of Oda fails to teach or suggest all of the elements of the claimed methods. Accordingly, Claims 1 to 28 are not obvious under 35 U.S.C. § 103(a) over Freidman (U.S. Patent No. 6,139,861) in view of Oda et al. (U.S. Patent No. 5,725,874) and this rejection may be withdrawn.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, reference no. TOPI-002CIP.

Respectfully submitted,

Date: October 5, 2007

By: _____
Bret E. Field
Registration No. 37,620

encs:

- Galer & Dworkin, A Clinical Guide to Neuropathic Pain (McGraw-Hill, 2000)
- Galer BS, Gammaitoni A, Alvaraz, N. Pain. Scientific American Medicine, WebMD. 2001, Chapter 10, Section XIV Bonica's Management of Pain (Lippincott Williams & Wilkins, 2001)
- Radcliffe Letter to the FDA
- http://www.maxfaxsho.co.uk/index_files/Page4811.htm

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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